Modulating microcircuits in depression

SUMMARY

Major depressive disorder (MDD) is globally the leading cause of disability with a worldwide prevalence of 4.4 %, affecting 322 million people in 2015. For the diagnosis of MDD, according to the Diagnostic and Statistical Manual of Mental Disorders number 5 (DMS-5), five of the following symptoms need to be present: a depressed mood, anhedonia, insomnia or hypersomnia, psychomotor retardation or agitation, loss of energy or fatigue, worthlessness or guilt, change in weight or appetite, impaired concentration or indecisiveness, and thoughts of death or suicidal ideation or an attempt. The treatment of MDD include antidepressant medication and psychological therapies. However, approximately one-third of treated patients do not respond adequately to these treatments. These patients suffer from treatment-resistant depression (TRD) which is associated with more hospitalizations and past suicide attempts. For TRD, different therapies modalities can be given such as electroconvulsive therapy (ECT), vagal nerve stimulation (VNS), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). In this thesis we have focused on deep brain stimulation in TRD, if we can disentangle TRD into different microcircuits, how we can improve clinical DBS outcomes and if we can refine DBS with a non-invasive technique called magnetothermal DBS introducing nanomaterial-mediated neuromodulation.

Chapter 1 is a general introduction into the theme and aims of this thesis. It gives information about major depressive disorder, treatment-resistant depression, current treatment options such as DBS and our view of possible microcircuits responsible of different traits in TRD. It provides our research questions and outline of this thesis.

Chapter 2 provides a narrative review of recent studies investigating the effectiveness of DBS in TRD. We especially focus on the relationship between the targeted brain structures and clinical outcomes. It discusses the importance of clinical subtypes of TRD. We concluded that precise evaluations of symptoms, biomarkers, and resting-state connectivity patterns are essential when distinguishing clinical subtypes of TRD. Subtyping TRD may provide more insight into the working mechanisms of DBS and help in selecting optimal targets in patients allowing for more personalized symptom-based treatment approaches.

Chapter 3 aimed to investigate different microcircuits within the prefrontal cortex of rats in an model of depression. We hypothesized that different microcircuits cause different behavioral traits in depressive-like behavior, and therefore, the treatment of depression and depressive traits lies in the modulation of different neural microcircuits. In this study, we found that High frequency (HF) DBS in the prelimbic (PreL) cortex but not the infralimbic (IL) cortex alleviated anhedonia and behavioral despair revealed by the sucrose preference and forced swim tests, respectively. These results suggest that modulation of specific sub-regions with its own microcircuits in the prefrontal cortex might be a potential approach towards providing tailored DBS therapy for different subtypes of depression.

Chapter 4 presents the adverse side-effects when stimulating a different subregion in the prefrontal cortex named the dorsal peduncular (DP) cortex. Stimulation in this DP subregion caused acute induction of seizures in ~40% of stimulated animals. Clinically relevant stimulation parameters were applied. We therefore conclude that the DP subregion of the vmPFC is not a suitable target to conduct DBS in mood disorders. It emphasis that the region for stimulation should be chosen carefully and that nearby brain structures can give rise to adverse side-effects.

Chapter 5 provides a review in which we describe and evaluate advanced techniques of neuromodulation of the brain and their latest refinements incorporating the usage of nanoparticles. We emphasize on DBS and magnethothermal deep brain stimulation (mDBS) using magnetic nanoparticles (MNPs) for nanomaterial-mediated neuromodulation. We conclude the application of MNPs as transducers of magnetic field into thermal, electrical, mechanical or chemical stimuli offers a possibility to remotely and wirelessly modulate specific groups of cells in arbitrarily deep regions of the brain.

Chapter 6 presents a study of mDBS in awake, freely moving mice done in collaboration with the research group of prof. dr. P. Anikeeva at the research laboratory of electronics (rle) at the Massachusetts Institute of Technology (MIT) (Boston, USA). We found that unilateral subthalamic nucleus (STN) mDBS in mice injected with MNPs results in more contralateral rotations around the body axis when compared to mice injected with non-MNPs. This results showed that mDBS in mice works and offers opportunities to further explore this techniques in various animal models of neuropsychiatric, neurosensory and neurodegenerative disorders.

Chapter 7 describes endogenously transient receptor potential vanilloid subtype-1 (TRPV1) expression in the human cingulate gyrus (CG) and medial frontal gyrus (MFG). Thus far, TRPV1 is needed for mDBS and has shown to be present in the CG and MFG of humans, albeit more in glial cells than in neurons. The potential use of endogenously TRPV1 for neuromodulation seems restricted. However, endogenously glial expression of TRPV1 may indicate an alternative approach for neuromodulation.

Chapter 8 summarizes the main findings in this thesis and provides answers to our research questions formulated in chapter 1. It addresses the limitations of our studies and future perspectives.